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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,831	11/30/2006	Maria Kavallaris	69544-2	2175

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,831	KAVALLARIS, MARIA	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/1/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 9 and 16-17 are pending.

2. Applicant's election of Group II, claim 9 (now claims 9 and 16-17 directed to a method for inducing in a cell a resistance to an anti-microtubule agent comprising the step of providing in a cell, a mutant g actin, filed on 5/1/08, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 9 and 16-17 are under examination as they read on a method for inducing in a cell a resistance to an anti-microtubule agent comprising the step of providing in a cell, a mutant γ actin.

4. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 16, Table on lines 13-14; page 33, lines 28-29; page 37, lines 32, 35 and 32 and page 38, line 1 has described several sequences that each must have a sequence identifier. Correction is required.

5. The specification on page 37 is objected to for the following informalities: page 37, line 4, the word "in" should be "is". Correction is required.

6. The Verrills et al. J Biol Chem. 2003 Nov 14;278(46):45082-93, cited on the PTO-892 was listed on the Australian Patent Office search report.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inducing in a cell a resistance to the antimicrotubule agent desoxyepothilone B or vinblastine, comprising the step of providing in a cell a mutant γ actin has the amino acid sequence of SEQ ID NO: 6 or 7; does not reasonably provide enablement for a method for inducing in a cell a resistance to any antimicrotubule agent" comprising the step of providing in a cell any "mutant γ actin" in claim 9, wherein the mutant g actin has a sequence shown in SEQ ID NO: 6 wherein residue number 103 is leucine in claim 16 or SEQ ID NO: 7, wherein residue number 98 is leucine in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and usethe invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404

(Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Claim 9, recites that use of any mutant γ actin to induce a resistance to any anti-microtubule agent. The specification on page 3, lines 19-31 discloses that the substitutions in regions of γ actin are located in sub domain I and sub domain IV of γ actin. Importantly, it is recognized that these amino acid substitutions may indeed control or contribute to resistance to anti-microtubule agents such as vinblastine and desoxyepothilone B, because they are located either in close spatial relationship to the ATP binding cleft of sub domain IV, or in sub domain I. The specification on page 38, under section 4, discloses that modeling of the γ–actin mutations revealed that D187--->H187 resides within subdomain IV. The V103→L103 mutation lies within subdomain I. This is thought to be the site of various actin-binding proteins. While the specification on page 40, lines 36-38 discloses that the P98L mutant is over 3-fold ($P<0.05$) and V103L mutant is over 2-fold resistance ($P<0.05$) to VLB compared to the empty vector and wildtype γ-actin cells, however, the specification on page 41, lines 6-4 discloses that the T162M and D187H mutants exhibit similar survival as the control cells. The specification demonstrates only specific mutants affect the cell resistance to anti-microtubules agent vinblastine and desoxyepothilone B, but not every substitution/mutation will affect the cell resistance to anti-microtubule agents. Therefore, absent the ability to predict which of γ-actin mutants would function as claimed for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Also, at issue is whether the γ-actin mutant would induce the resistance to any anti-microtubule agent. Given that Applicant demonstrated that the P98L and V103L mutants induce resistance to VLB compared to the empty vector and wildtype γ-actin cell. Moreover, given that microtubule targeting agents can "disrupt" microtubules quite readily in vitro using purified tubulin that lacks any actin (see Fojo T, J. Natl. Caner Institute, 98(19), 2006). It cannot be seen how to apply the claimed method to any anti-microtubule agents that do not require actin for their action. Schaefer In Expert Opinion on Investigational Drugs (July 2007, Vol. 16, No. 7, Pages 923-926) teaches PPAR-γ inhibitors were shown to reduce tubulin levels without affecting the polymerization of tubulin *in vitro* (see Abstract). It is not predictable whether γ-actin would play a role with such anti-microtubule inhibitors.

Given that the specification demonstrated that the method worked for VLB and dEpoB, then applicant is enabled for those two anti-microtubule agents. It is noted that the specification discloses that the nature of this mechanism(s) is not understood (see page 1, lines 29-30). The specification further discloses that this is the first report of γ-actin mutations associated with drug resistance. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971).

However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. See MPEP 2164.03.

Further at issue is that the claimed method reads on cells *in vivo*. There must be a rigorous correlation of pharmacological activity between the disclosed *in vitro* activity and an *in vivo* activity to establish practical activity. However, given the relatively incomplete understanding in correlating *in vitro* assays and *in vivo* animal models to clinical treatment of cancer involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, the claims are not enabled. See MPEP 2164.08.

"Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." Ex parte Maas, 9 USPQ2d 1746.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 9 and 16-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of for an *in vitro* method for inducing in a cell a resistance to the antimicrotubule agent desoxyepothilone B or vinblastine, comprising the step of providing in a cell a mutant γ actin has the amino acid sequence of SEQ ID NO: 6 or 7.

Applicant is not in possession of for a method for inducing in a cell a resistance to any antimicrotubule agent" comprising the step of providing in a cell any "mutant γ actin" in claim 9, wherein the mutant g actin has a sequence shown in SEQ ID NO: 6 wherein residue number 103 is leucine in claim 16 or SEQ ID NO: 7, wherein residue number 98 is leucine in claim 17.

The Examiner directs Applicant's attention to Examples 10 and 11, in the resent published Written Description Training Materials, March, 25, 2008. In particular, claim 3 in Example 10.

Applicant has disclosed only amino acid of SEQ ID NO: 6 and 7 mutants; therefore, the skilled artisan cannot envision all the contemplated γ-actin mutant possibilities recited in the instant claims. There is no art-recognized correlation between any structure (other than SEQ ID NO: 6 or 7) and the activity of inducing resistance to an anti-microtubule agent, base on which those of ordinary skill in the art could predict which amino acids can mutat from SEQ ID NO: 5. There is no information about which amino acids can mutat from SEQ ID NO: 5 in the claimed genus of mutant γ actin and still retain the induce resistance to anti-microtubule agent.

Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(f) he did not himself invent the subject matter sought to be patented

11. Claims 9 and 16-17 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter (see Po'uha 2006).

Dr. Po'uha's dissertation entitled "Role of Actin and its Regulating Proteins in Drug

Response" has described the claimed invention. Dr. Po'uha describes a method for inducing in a cell a resistance to an anti-microtubule agent comprising the step of providing in a cell a mutant γ actin. In particular, Po'uha described γ-actin mutations in drug resistance (see Fig. 1.1). Clonogenic assay plate showing that the cells expressing mutant γ-chain have increased clonogenic survival in the presence of vinblastin, indicating resistance to vinblastin, wherein the mutant γ-actin is SEQ ID NOs: 6 or 7 (see page 19). It is generally accepted that a doctoral candidate must exhibit original and independent research as evidenced by their thesis to fulfill the requirements for the degree of Ph.D. The thesis is published only under the name of the Po'uha, who must be presumed to be largely responsible for the work obtained therein.

Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventor of the claimed invention. To resolve the ambiguity, applicants may file a declaration by the non-applicant Po'uha, who appears to have conceived and conducted the claimed subject matter in the thesis, entitled "Role of Actin and its Regulating Proteins in Drug Response".

Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing, which would lead to a reasonable conclusion that applicant Maria Kavallaris is the sole inventor of the claimed invention.

11. Claims 9 and 16-17 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter (see Verrills, N. M 2004).
Verrills, N. M. (2004). Mechanisms of Resistance to Anti-microtubule Agents in Childhod Leukaemia, Doctor of Philosophy, Macquarie University, Sydney, NSW, Australia.

Dr. Verrills' dissertation entitled "Role of Mechanisms of Resistance to Antimicrotubule agents in Childhod Leukaemia" has described the claimed invention. Dr. Verrills describes a method for inducing in a cell a resistance to an anti-microtubule agent comprising the step of providing in a cell a mutant γ actin. In particular, Po'uha described γ-actin mutations in drug resistance (see Fig. 1.1) referring to Dr. Verrills dissertation. Clonogenic assay plate showing that the cells expressing mutant γ-chain have increased clonogenic survival in the presence of vinblastin, indicating resistance to vinblastin, wherein the mutant γ-actin is SEQ ID NOs: 6 or 7 (see page 19). It is generally accepted that a doctoral candidate must exhibit original and independent research as evidenced by their thesis to fulfill the requirements for the degree of Ph.D. The thesis is published only under the name of the Verrills, who must be presumed to be largely responsible for the work obtained therein.

Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventor of the claimed invention. To resolve the ambiguity, applicants may file a declaration by the non-applicant Verrills, who appears to have conceived and conducted the claimed subject matter in the thesis, entitled "Role of Mechanisms of Resistance to Antimicrotubule agents in Childhod Leukaemia".

Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing, which

would lead to a reasonable conclusion that applicant Maria Kavallaris is the sole inventor of the claimed invention.

12. The Verrills et al (J Natl Cancer Inst. 2006 Oct 4;98(19):1363-74) reference cited on the PTO-892 for its teachings that N.M Verrills and S. T. Po'uha contributed equally to the work. Further, Verrills et al indicates that N.M Verrills and M. Kavallaris hold a patent related to the identified γ-actin mutations described in this article (Australian patent AU2004/000331 (claimed as prior document in the instant application), USA), which corresponds to WO 2004/083239. However, WO 2004/083239 list only M. Kavallaris as the inventor.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 16, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644